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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
LIU, SAMUEL W	
ART UNIT	**PAPER NUMBER**
1653	

DATE MAILED: 01/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/601,667	MORRIS ET AL.	
	Examiner	Art Unit	
	Samuel W Liu	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 August 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *49,52 and 54-90* is/are pending in the application.

4a) Of the above claim(s) *46-48,55-77 and 81-90* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *49, 51, 54 and 78-80* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The response filed 14 August 2003, which amends claims 49, 51, 78 and 80, and cancels claims 50, 52 and 53, and applicants' request for extension of time of one month, have been entered.

The following pending claims 49, 51, 54 and 78-80 are examined in this Office action. Note that the grounds of objection and/or rejection not explicitly stated and/or set forth below are withdrawn.

Also, note that the examiner has required restriction between product (claims 49, 51, 54 and 78-80 of the instant application) and process claims (e.g., claims 46-48 of the current application). Where applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04. Process claims that depend from or otherwise include all the limitations of the patentable product will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112. Until an elected product claim is found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process

claims that are not commensurate in scope with an allowed product claim will not be rejoined. See "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C. § 103(b)," 1184 O.G. 86 (March 26, 1996). Additionally, in order to retain the right to rejoinder in accordance with the above policy, Applicant is advised that the process claims should be amended during prosecution either to maintain dependency on the product claims or to otherwise include the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder.**

Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

The following is a new ground of the rejection

Claim Rejections - 35 USC § 101

35 U.S.C. §101 states:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title.

Claims 49, 51, 54 and 78-80 are rejected under 35 USC 101 because the claimed invention is directed to non-statutory subject matter.

Claims 49, 51, 54, and 78-80, as written, do not distinguish the claimed polypeptides from naturally existing products. The claims do not particularly point out any differences indicating the hand of man. In the absence of the hand of man, the claimed products are considered non-statutory subject matter. *See Diamond v. Chakrabarty*, 447 U.S. 303, 206 USPQ

193 (1980). The claims should be amended to indicate the hand of the inventor, *e.g.*, by insertion of "isolated" or "purified".

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter that the applicant regards as his invention.

Claims 49 and 51 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 49 recites "or a fragment thereof"; the recitation is unclear as to whether or not said fragment refers to any fragment including dipeptide comprising phenylalanine residue. Note that the specification does not define fragment thereof.

Claim 51 also recites "or a fragment thereof"; the recitation is unclear for the same reasons stated above and as to whether or not said fragment of the sequence SEQ ID NO:3 comprises residue 264 (the C-terminal residue) because the carboxyl terminus of the mistletoe lectin polypeptide is important for biological function of the polypeptide.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 49, 51 and 78-80 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for mistletoe lectin polypeptides of SEQ ID NOs: 1, 3-4, 6-11, 38 and 40-41 and a pharmaceutical composition comprising the polypeptides thereof, does not reasonably provide enablement for a fragment of SEQ ID NO:1 (claim 49), or SEQ ID NO:3 (claim 51), and pharmaceutical composition comprising the polypeptide thereof (claims 78-80). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The application disclosure and claims have been compared per the factors indicated in the decision *in re* Wands 8 USPQ2d 1400, 1400 (Fed. Cir. 1998). These factors are considered when determining whether there is sufficient evidence to support a description that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. The factors include but not limited to: 1) the nature of the invention; 2) the breath of the claims; 3) the predictability or unpredictability of the art; 4) the amount of direction or guidance presented; 5) the presence or absence of working examples; 6) the quantity of experimentation necessary; 7) the relative skill of those skilled in the art.

Each factor applicable is addressed below on the basis of comparison of the disclosure, the claims and the state of the prior art in the assessment of undue experimentation.

(1) The scope of the claims/(2) The nature of the invention:

The claims set forth a fragment of the full-length sequences (SEQ ID NO: 1 or 3), which encompass large numbers of structural variants, i.e., deletions, truncation, rearrangements and/or chemical modifications in the amino acid sequence of full-length polypeptide. These structural

variants represent a divergence from a core or a motif structure, which has not been described in the specification. Thus, physical structure and chemical and biological properties are undefined and lead to undue experimentation in defining these characteristics. The specification only describes how to make and use the mistletoe lectin polypeptides, e.g., full-length SEQ ID NOs:1 and 3. The specification does not reasonably provide guidance and working examples as to how to make the bioactive variants. Therefore, the scope of claims is outside the bounds of the enablement and would have resulted in the necessity of undue experimentation.

(3) The unpredictability of the art:

The claimed invention is directed a large number of the variant polypeptides or subsequences thereof. The current claim language of " a fragment thereof " broadly encompasses a variety of both genetic mutants (*i.e.*, naturally-occurring variants), *e.g.*, RNA-editing and mRNA-splicing products which are result from genetic deletion, insertion and sequence exchanging event (see page 5, lines 1-7). Without characterization each polypeptide or peptide variant, biological activity of the variant or fragment thereof is unpredictable in view of structure and function.

The specification sets forth that the pharmaceutical composition comprising the polypeptide that possesses catatonic activity and has capability of recognize and bind to peptide hormone in the target (see page 19, 3rd paragraph). Yet, the specification does not provide guidance or working examples regarding how to make and use the fragments of the polypeptides. Note that the claimed polypeptide is a glycoprotein which requires posttranslational modification. Since the posttranslational modification, e.g., a specific glycosylation depends upon a particular amino acid sequence or motif(s) within the polypeptide thereof; the disclosure needs to provide description for

supporting enablement. Eck, J. et al. (*Eur. J. Biochem.* (1999) 265, 788-797) teach that the different molecular weight of mistletoe lectins have varied degree of glycosylation and glycosylation may influence biological activity of the lectin polypeptide (see page 788, the right column and page 796, the left column). Moreover, disulfide linkage involves in maintaining ternary structure and thereby plat a role in biological activity of the lectin protein composed of multiple subunits (see Niwa, H. et al. (2003) *Eur. J. Biochem.* 270, 2739-2749, especially "Discussion" section). Thus, in the absence of teaching or guidance with regard to (i) whether or the polypeptide fragments comprise specific glycosylation site(s) or/and sulfhydryl groups that participate in the disulfide linkage formation, and (ii) how to make and use the lectin polypeptide fragments or variants, predicting what changes can be made to the claimed polypeptide so that the variant molecules have improved or at least retain apparent binding activity mentioned supra after deletion, or truncation, or/and rearrangements, and/or chemical modifications in the amino acid sequence of the parent peptides is unpredictable. In re Fisher, 166 USPQ 18 indicates that the more unpredictable an art area is, the more specific enablement is necessary in order to satisfy the statute.

(4) The state of the prior art:

The general knowledge and level of skilled in the art do not supplement the omitted description. Specific, not general, guidance is what is needed. The disclosure fails to describe common attributes and characteristics that identify agent(s) for cardiac therapy. The genus is highly variant, the specification needs to provide sufficient guidance to be considered enabling but does not.

The current disclosure and state of the art records do not provide the minimum sequence in length and structural motif or core sequence in order to at least maintain fundamental activity of the mistletoe lectin polypeptide variants compared with that of the full-length polypeptide of SEQ ID NOs:1 or 3, the skilled artisan would not know how to make and use the disclosed compositions.

(5) The quantity of experimentation necessary:

In the absence of working examples with regard to the genus stated above, unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take undue trials and errors to practice the claimed invention. The quantity of experimentation would be large and unpredictable. One skilled in the art would be required to carry out an undue experimentation for screening and characterizing the peptide analogs that have membrane-permeability, membrane-affinity, target specificity, and potent antimicrobial activity.

(6) The relative skill of those in the art:

The general knowledge and level of skill in the art do not supplement the omitted description with respect to a massive number of variant sequences of the polypeptide. In view of the preceding factors (1-5), the level of skill in this art is high and is at least that of a microbiologist with several years of experience in molecular biology as well as knowledge in peptide chemistry, synthesis and pharmacology. Even with a level of skill in the art as mentioned above, predictability of results is still highly variable. An undue level of experimentation is needed on the part of the skilled artisan in order to identify the cytotoxic lectin protein that are generated from modification, *e.g.*, deletion, or truncation, or/and rearrangement – genetically or

recombinantly, or, chemical modification which includes (i) post-translational modification (e.g., phosphorylation, ubiquitination, lipidation, and/or intra- or/and inter-disulfide formation) and (ii) *in vitro* chemical modification, *e.g.*, alkylation and domination, and test for their ability of recognizing molecule, e.g., peptide hormone, on target cells, and in order to formulate/use the pharmaceutical composition comprising the polypeptide fragment thereof for treating uncontrolled cell growth, e.g., cancer (see page 20, the 3rd paragraph of the specification).

In consideration of each of factors stated above, absent factual data to the contrary, the amount and level of experimentation needed is undue.

Claim Rejections - 35 USC §102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 49 and 51are rejected under 35 U.S.C. 102(e) as being anticipated by Lentzen, H. et al. (US Pat. No. 6271368).

Lentzen et al. teach a polypeptide sequence of SEQ ID NO:43 comprising a fragment (amino acid 172-262) that reads on the protein of SEQ ID NO:3 (amino acid residues 183-263). Because the current claim language "a fragment" is open-ended, and because the recitation "said fragment exhibits cytotoxic and/or immunostimulatory activity" has no patentable weight *per se* associated with the use of the claimed polypeptide and biological activity will not be altered due to the use of the polypeptide thereof, Lentzen et al. teaching anticipates the application claim 51. The above Lentzen et al. teaching also anticipates the application claim 49 because the recitation of claim 49 "a fragment of sequence of (i) [*i.e.*, SEQ ID NO:1] wherein said fragment comprises a phenylalanine" reads on any peptide fragment comprising phenylalanine (Phe), and because Lentzen's polypeptide stated above comprises Phe at position 219 (i.e., amino acid residue 219).

Claims 49 and 51are rejected under 35 U.S.C. 102(b) as being anticipated by Borgnia, M. J. et al. (J. Biol. Chem. (1996) 271, 3163-3171).

Borgnia et al. teach a cytotoxic agent, i.e., a chemically modified dipeptide: *f-NLP-ME* (N-formyl-methiony-leucyl-phenylalanyl-methylester) (see page 3164, the right column, "Discussion" section), which meets the limitation set forth in the application claim 49, items iii) and iv) and the limitation set forth in the application claim 51. Note that since the specification does not explicitly define what the fragment is, the recited fragment encompasses any peptides (including dipeptide) or polypeptides.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel Wei Liu whose telephone number is (703) 306-3483. The examiner can normally be reached from 9:00 a.m. to 5:30 p.m. on weekdays. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Christopher Low, can be reached on 703-308-2923. The fax phone number for the organization where this application or proceeding is assigned is 703 308-4242 or 703 872-9306 (official) or 703 872-9307 (after final). Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 305-4700.

SWL

Samuel Wei Liu, Ph.D.

December 16, 2003

Christopher S. F. Low

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